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Intellectual Property Department
FibroGen, Inc.
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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/040,204	KIVIRIKKO ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 24-57 is/are pending in the application.

4a) Of the above claim(s) 37-57 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 24-36 is/are rejected.

7)☒ Claim(s) 24-36 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 19 December 2001 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 0602;0602.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 24-57 are pending.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121 and 372:

I. Claims 24-36, 38-50, 52, and 56, drawn to host cells transfected with a polynucleotide encoding human collagen and a polynucleotide encoding a prolyl 4-hydroxylase, classified in class 435, subclass 254.2.

II. Claims 37, 51, and 57, drawn to methods for producing recombinant collagen, classified in class 435, subclass 71.1.

III. Claims 53-55, drawn to a recombinant human collagen, classified in class 530, subclass 356.

For each of inventions I-III above, restriction to one of the following is also required under 35 USC 121 and 327. Therefore, election is required of one of inventions I-III and one of inventions (A)-(P).

(A). Collagen type IV.

(B). Collagen type V.

(C). Collagen type VI.

(D). Collagen type VII.

(E). Collagen type VIII.

(F). Collagen type IX.

(G). Collagen type X.

(H). Collagen type XI.

(I). Collagen type XII.

(J). Collagen type XIII.

(K). Collagen type XIV.

(L). Collagen type XV.

(M). Collagen type XVI.

(N). Collagen type XVII.

(O). Collagen type XVIII.

(P). Collagen type XIX

Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). Also, product and process inventions are distinct if any of the following can be shown: (1) that the process as claimed can be used to make another and materially different product, (2) that the product claimed can be used in a materially different process of using that product, or (3) that the product claimed can be made by another and materially different process (MPEP § 806.05(h)). These inventions are different or distinct for the following reasons.

The methods of Invention II are related to the host cells of Invention I as a product and process of using. The inventions are distinct because the host cells can also be used for production of the prolyl 4-hydroxylase enzyme.

The host cells of Invention I are related to the collagen product of Invention III by virtue of the host cells synthesizing the collagen. Although the host cells and collagen product are related, they are distinct inventions because they are physically and functionally distinct

chemical entities, and the collagen product can be made by another and materially different process, such as by purification from the natural source. Further, the host cells may be used for processes other than the production of collagen, such as production of the prolyl 4-hydroxylase enzyme.

The methods of Invention II are related to the collagen products of Invention III as process of making and product made. The inventions are distinct because collagen can be made by isolating it from a natural source.

Inventions (A)-(P) are distinct because they represent structurally different polypeptides or host cells transfected with polynucleotides encoding the structurally different polypeptides. Therefore, where structural identity is required, such as for protein expression, the different host cells have different effects.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art due to their recognized divergent subject matter, as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Leanne Price's representative, James Nesbitt, on June 25, 2004, a provisional election was made with traverse to prosecute Invention I, Claims 24-36. Affirmation of this election must be made by applicant in replying to this Office action. Claims 37-57 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The Examiner has required restriction between product and process claims. Applicant has elected claims directed to the product. If a product claim is subsequently found allowable, withdrawn process claims, that depend from or otherwise include all the limitations of the allowable product claim, will be rejoined in accordance with the Official Gazette notice dated March 26, 1996 (1184 O.G. 86; see also M.P.E.P. 821.04, *In re* Ochiai, and *In re* Brouwer). Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right, if the amendment is presented prior to final rejection or allowance, whichever is earlier. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. To be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112.

FIRST ACTION ON THE MERITS

Specification-Objections

The first paragraph of the specification, wherein the benefit of priority is claimed, should be corrected to reflect the current status of prior applications i.e. issued or abandoned where appropriate.

The specification is objected to for stating (pg 58, lines 12-13) that data representing the amount of collagen type III expressed in host cells are presented in Table II. Table II does not contain said data, it presents data on the enzymatic activity of expressed prolyl 4-hydroxylase.

The specification is objected to for being confusing in the description of the data presented in Table III. On page 58, lines 26-30, the specification states that "The highest type III

collagen expression values were in the High Five cells that also expressed prolyl 4-hydroxylase, the type III collagen in these cells being about 41-81 μg/5 x 10^6 cells (Table III)". However, the title for Table III is "Prolyl 4-hydroxylase activity....". Furthermore, the data of Table III are presented as dpm/10 μl and, therefore, are not consistent with the units presented in the text i.e. μg/5 x 10^6 cells. Clarification is required. For purposes of examination, it is assumed that the data of Table III represents expression of collagen type III, as assayed by radioimmunoassay and expressed as dpm/10 μl.

The specification is objected to for having inconsistent formatting of the tables. For example table 2 is presented as "Table 2", while table 3 is presented as "Table III". Correction is requested.

The specification is objected to for having a blank space on page 71. Correction is requested.

On page 56, line 36, "treatment of after" should be changed to "treatment or after". On page 66, line 3, "ascorbate of prolyl" should be changed to "ascorbate or prolyl".

The specification should be carefully check and any spelling or grammatical errors corrected. Blank spaces should be deleted.

Figures

Figures 1, 5, and 8 are objected to for not having the Y-axis labelled. Correction is required.

Information Disclosure Statement

The Information Disclosure Statement of June 20, 2002 is objected to because references 13, 62, 63, and 82 are either not complete or not correct.

References 8, 13, 24, 39, 46, 47, 62, 63, and 82 of the Information Disclosure Statement of June 20, 2002 are not available to the Examiner and have not been considered. If Applicants wish for said references to be considered, new copies should be submitted.

Claims-Objections

The claim set is objected to for not beginning with a sentence of which the claims are the object. For example, "We claim" or "The claims are". Correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

> The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
> A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
> Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claims 24-36 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-12 of US Patent 5,593,859. Although the

conflicting claims are not identical, they are not patentably distinct from each other. Claims 24-36 herein and Claims 1-12 of 5,593,859 are both directed to host cells comprising polynucleotides encoding a human collagen or procollagen and a prolyl 4-hydroxylase. The claims differ in that Claims 1-12 of 5,593,859 recite host cells wherein the polynucleotide encoding the collagen or procollagen encodes either type I, type II, or type III collagen or procollagen, while Claims 24-36 herein recite host cells wherein the polynucleotide encoding the collagen or procollagen encodes any collagen or procollagen. The portion of the specification in 5,593,859 that supports the recited host cells includes embodiments that would anticipate Claims 24-36 herein, e.g., host cells wherein the polynucleotide encoding the collagen or procollagen encodes any collagen or procollagen, which are anticipated by the host cells specifically recited in Claims 1-12 of 5,593,859. Claims 24-36 herein cannot be considered patentably distinct over Claims 1-12 of 5,593,859 when there are specifically recited embodiments (host cells wherein the polynucleotide encoding a collagen or procollagen encodes either type I, type II, or type III collagen or procollagen) that would anticipate Claims 24-36 herein. Alternatively, Claims 24-36 herein cannot be considered patentably distinct over Claims 1-12 of 5,593,859 when there are specifically disclosed embodiments in 5,593,859 that supports Claims 1-12 of that patent and falls within the scope of Claims 24-36 herein, because it would have been obvious to a skilled artisan to modify the methods of Claims 1-12 of 5,593,859 by selecting a specifically disclosed embodiment that supports those claims, i.e., host cells wherein the polynucleotide encoding a collagen or procollagen encodes either type I, type II, or type III collagen or procollagen, as disclosed in 5,593,859. One having ordinary skill in the art would have been motivated to do this, because such an embodiment, host cells wherein the polynucleotide encoding a collagen or

procollagen encodes either type I, type II, or type III collagen or procollagen, is disclosed as being a preferred embodiment within Claims 1-12 of the prior patent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Although Claim 32 is recited as dependent from Claim 24, it is believed that Claim 32 is meant to be dependent from Claim 31. For purposes of examination, it is assumed that Claim 32 is meant to be dependent from Claim 31. Clarification is requested.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In this regard, the application disclosure and claims are compared per the factors indicating in the decision re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4)

the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Enablement

Claims 24-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for host cells comprising a polynucleotide encoding human type I, type II, or type III collagen and a polynucleotide encoding human prolyl 4-hydroxylase, does not reasonably provide enablement for a host cell comprising both a polynucleotide encoding any protein having the properties of a collagen and a polynucleotide encoding any protein having prolyl 4-hydroxylase activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 24-36 are so broad as to encompass host cells comprising both a polynucleotide encoding any protein having the properties of a collagen and a polynucleotide encoding any protein having prolyl 4-hydroxylase activity. The scope of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides encoding any protein with the properties of a collagen and the extremely large number of polynucleotides encoding any protein with prolyl 4-hydroxylase activity. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of the structure for those proteins have the desired as well as changes that can be tolerated in any protein with the desired activity requires a knowledge of and guidance with

regard to which amino acids in the protein's sequence are necessary for the desired activity/function and which residues, if any, are tolerant of modification and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to host cells comprising a polynucleotide encoding human type I, type II, or type III collagen and a polynucleotide encoding human prolyl 4-hydroxylase.

While recombinant and mutagenesis techniques as well as assays for collagen-like function and prolyl 4-hydroxylase activity are known, it is not routine in the art to screen unlimited numbers of polynucleotides for encoding proteins with the desired function or activity or to screen for multiple substitutions or multiple modifications of proteins with the desired function or activity, as encompassed by the instant claims. Furthermore, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the Claims 24-36, which encompasses host cells comprising a polynucleotide encoding any human protein with collagen function and a polynucleotide encoding any protein with prolyl 4-hydroxylase activity. The specification does not support the broad scope of Claims 24-36 because the specification does not establish: (A) any polynucleotides encoding any protein with the function of collagen, other than polynucleotides encoding human collagen type I-IV, XIII, and XVIII; (B) regions of the protein structure which may be modified without effecting the function of human collagen type

I-IV, XIII, or XVIII; (C) the general tolerance of the function of human collagen type I-IV, XIII, and XVIII to modification and extent of such tolerance; (D) a rational and predictable scheme for identifying any protein with collagen function or for modifying any residues of collagen type I-IV, XIII, and XVIII with an expectation of obtaining the desired biological function; (E) any polynucleotides encoding any protein with prolyl 4-hydroxylase activity, other than polynucleotides encoding human prolyl 4-hydroxylase; (F) regions of the protein structure which may be modified without effecting the activity of human prolyl 4-hydroxylase; (G) the general tolerance of the activity of human prolyl 4-hydroxylase to modification and extent of such tolerance; (H) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (I) the specification provides insufficient guidance as to which of the essentially infinite possible choices of polynucleotide encoding proteins with collagen function or the essentially infinite possible choices of polynucleotides encoding proteins with prolyl 4-hydroxylase activity are likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of host cells comprising any number polynucleotides encoding a protein with collagen function and any number of polynucleotides encoding a protein with prolyl 4-hydroxylase activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and

improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claims 24-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of host cells comprising one of a genus of polynucleotides encoding any human protein with collagen function and one of a genus of polynucleotides encoding any protein with prolyl 4-hydroxylase activity. The specification teaches only three species of such host cells, teaches the structure of only six such polynucleotides encoding human collagens, and only a single representative species of polynucleotides encoding a protein with prolyl 4-hydroxylase activity. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a protein with collagen function or encoding a protein with prolyl 4-hydroxylase activity. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 24-28, and 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Prockop et al, 1993 (WO 93/07889; IDS). Prockop et al teach recombinant host cells comprising a transfected polynucleotide encoding a human procollagen or collagen and a transfected polynucleotide encoding prolyl 4-hydroxylase (pg 4, lines 10-15). Said host cells include eukaryotic cells, insect cells (Example 7), yeast cells, *P. pastoris* cells (Example 9), *S. cerevisiae* cells (Example 8), and mammamlian cells (Example 1). Therefore, Claims 24-28, 30, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Prockop et al, 1993.

Claims 24-28, and 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Prockop et al, 1997 (US 5,593,859; IDS). Prockop et al teach recombinant host cells comprising a transfected polynucleotide encoding a human procollagen or collagen and a transfected polynucleotide encoding prolyl 4-hydroxylase (col 2, lines 58-63; Claims 1-23). Said host cells include eukaryotic cells (Claim 22), insect cells (Claim 9), yeast cells (Claim 10), *P. pastoris* cells (col 5, lines 40-45), *S. cerevisiae* cells (Claim 11), mammamlian cells (Claim 22), and non-human mammalian cells (Claim 19). Therefore, Claims 24-28, and 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Prockop et al, 1997.

Claims 24-27, 32-34 are rejected under 35 U.S.C. 102(e) as being anticipated by Bell et al, 2004 (priority date 10-NOV-2000). Bell et al teach recombinant host cells comprising a

transfected polynucleotide encoding a human procollagen or collagen and a transfected polynucleotide encoding prolyl 4-hydroxylase (parg [0057]). Said host cells include prokaryotic cells, eukaryotic cells, yeast cells, plant cells, and insect cells (parg [0055]). Therefore, Claims 24-27 and 33 are rejected under 35 U.S.C. 102(e) as being anticipated by Bell et al, 2004 (priority date 10-NOV-2000).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomita et al, 1995 in view of Veijola et al, 1994. Tomita et al teach Sf9 recombinant host insect cells comprising a transfected polynucleotide encoding a human collagen type III protein-α1(III) chain (Fig 1). Tomita et al do not teach a recombinant host cell comprising both a transfected polynucleotide for a human collagen or procollagen and a polynucleotide encoding prolyl 4-hydroxylase. Veijola et al teach Sf9 recombinant host insect cells comprising a transfected polynucleotide encoding prolyl 4-hydroxylase (pg 26749, parg 2; Fig 5). It would have been obvious to a person of ordinary skill in the art to make a recombinant Sf9 host insect cells comprising both a polynucleotide encoding a collagen or procollagen and a polynucleotide encoding prolyl 4-hydroxylase. To do so is suggested by Tomita et al wherein they state that the recombinant procollagen protein had a lower melting temperature than native procollagen III, which is due to an insufficiency of prolyl hydroxylase activity within the recombinant host cells

(Abstract; pg 852, parg 4). Motivation to combine the teachings of Tomita et al and Veijola et al to make a host cell that comprises polynucleotides for both collagen and prolyl 4-hydroxylase derives from the advantage of hydroxylating collagen, which is necessary for formation of trimeric fibrillar collagen. The expectation of success is high, as host cells comprising polynucleotides encoding collagen or prolyl 5-hydroxylase have been prepared; thus, one of skill in the art to expect success in making host cells comprising polynucleotides encoding both collagen and prolyl 5-hydroxylase. Therefore, Claims 10-12, 20, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Claims 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomita et al, 1995 in view of Veijola et al, 1994.

Claims 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hara et al, 1997 in view of Prockop et al, 1993 or Prockop et al, 1997. Hara et al teach an E. coli host cell comprising a polynucleotide encoding a collagen fusion protein (col 11, line 64-col 14 line 61). Hara et al do not teach an E. coli host cell comprising polynucleotides encoding both collagen and prolyl 4-hydroxylase. The teachings of Prockop et al, 1993 and Prockop et al, 1997 are described above. It would have been obvious to a person of ordinary skill in the art to combine the teachins of Hara et al with the teachings of Prockop et al, 1993 or Prockop et al, 1997 to prepare an E. coli host cell comprising polynucleotides for both a collagen fusion protein and prolyl 4-hydroxylase. Motivation to do so is provided by the following advantages of said E. coli host cell: (i) production of collagen as a fusion protein would allow for easy purification; (ii) use of E. coli host cells for production of fusion proteins is well known in the art; and (iii) coexpression of prolyl 4-hydroxylase would allow for purification of fibrillar collagen. The expectation of success is high, as E. coli host cells comprising a polynucleotide encoding a

collagen fusion protein are known in the art and eukaryotic host cells comprising polynucleotides for both collagen and prolyl 4-hydroxylase are known in the art. Therefore, Claims 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hara et al, 1997 in view of Prockop et al, 1993 or Prockop et al, 1997.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan Lee Swope, Ph.D.

REBECCA E. PRUITY
PRIMARY EXAMINER